ICH M14: General Principles on Planning, Designing, Analysing and Reporting of Non-interventional Studies That Utilise Real-World Data for Safety Assessment of Medicines

Step 4 document – to be implemented

September 2025

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

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Background

- **This document has been signed off as *Step 4* document (4 September 2025) to be implemented by the ICH Regulatory Members.**
- **This document was developed based on a Concept Paper (5 April 2022) and Business Plan (5 April 2022).**

Introductory Note

These slides were produced as training material to accompany the ICH M14 Guideline.

The intention is to assist the scientific community in the understanding of the new guideline to support the development of high-quality evidence regarding the safety of medicines to address regulatory questions.

For this purpose, the training material highlights selected sections of the guideline content, and for practicality purposes, is also accompanied by an example that is illustrative of the conceptual framework that was drafted based on the experience of the Expert Working Group members.

Training Objective

- **To understand the purpose, scope and considerations related to designing and executing non-interventional studies (NIS) fit for regulatory decision-making.**

  Key steps in the conceptual framework for designing and executing NIS are illustrated with a worked example.

Key Principles

- **Provides recommendations on the planning, designing, analysing, and the reporting of non-interventional studies that utilise fit-for-use data for assessment of medicines (drugs, vaccines, and other biological products)**
  - Guideline addresses safety evaluations, but the principles presented may apply to effectiveness studies when real-world data are included.
- **Outlines an evidence-based approach to the development of high-quality evidence regarding the safety of medicines to address regulatory questions**
  - Recommends an iterative approach to study development, focusing on assessment of data fitness for use, the application of feasibility assessments to guide study design, further refinement of design based on feasibility results.
  - Recommends interaction with regulators for key decisions throughout the process.
- **Emphasises the importance of prespecifying and documenting key decisions around exposure, outcome, and covariate definitions, analysis plans, data management, and other aspects.**
- **Encourages transparency in study conduct, reporting, and dissemination of results.**

Expected Benefits

- Address gap in harmonised guidance on the development, conduct, and implementation, and regulatory use of non-interventional studies utilising real-world data.
- Provide recommendations and high-level best practices for study conduct of these studies.
- Improve efficiency and transparency in the development, reporting, submission and review of non-interventional studies and resultant regulatory actions.
- Improve the ability of the study protocol and report to be accepted across regulatory authorities.

Summary of Guideline Content

- Emphasises the importance of **fit-for-use real-world data** to address specific research questions via a stepwise, **iterative process** for study design and data source selection.
- Recommends an integrated assessment to determine if the evidence generated will be adequate, based on:
  - Data **relevance** and **reliability**;
  - Appropriateness of study **design** and **analytic** methods;
  - Robust assessment of study **limitations** and their impact on validity of the findings.
- Provides recommendations for **protocol** development including considerations for data sources, study population, exposures/outcomes/covariates, comparators, bias and confounding, and validation. Importance of **prespecifying** and **documenting** key decisions is stressed.
- Early **engagement** with regulatory authorities is encouraged.
- Emphasis is placed on **transparency** in study conduct, reporting, and dissemination of results.
- **Target audience** includes regulatory agencies, sponsors of non-interventional studies, researchers/study teams, data source holders/owners, public health organizations/agencies, scientific journals/outlets for dissemination.

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Considerations at Study Kickoff

- Align on research question & study objective(s);
- Identify appropriate subject matter experts;
- Identify and plan for key stakeholder engagement (e.g., health authority(ies));
- Define key milestones and timelines (e.g., protocol/statistical analysis plan (SAP) finalization, final report);
- Identify known or anticipated risks to study design, execution; plan mitigation strategies;
- Clarify operational aspects including meeting logistics for the study team (frequency, decision log, etc.).

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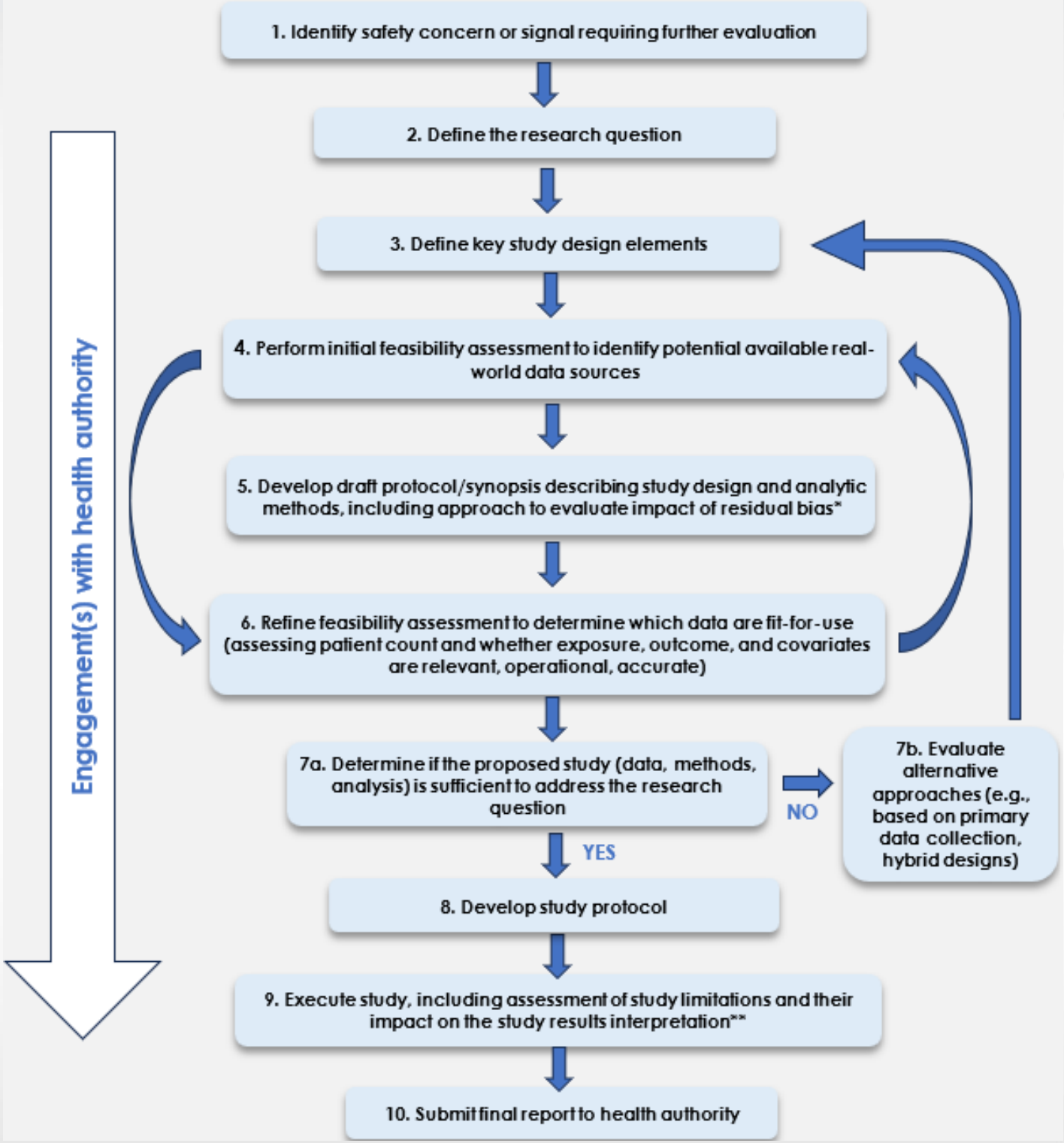
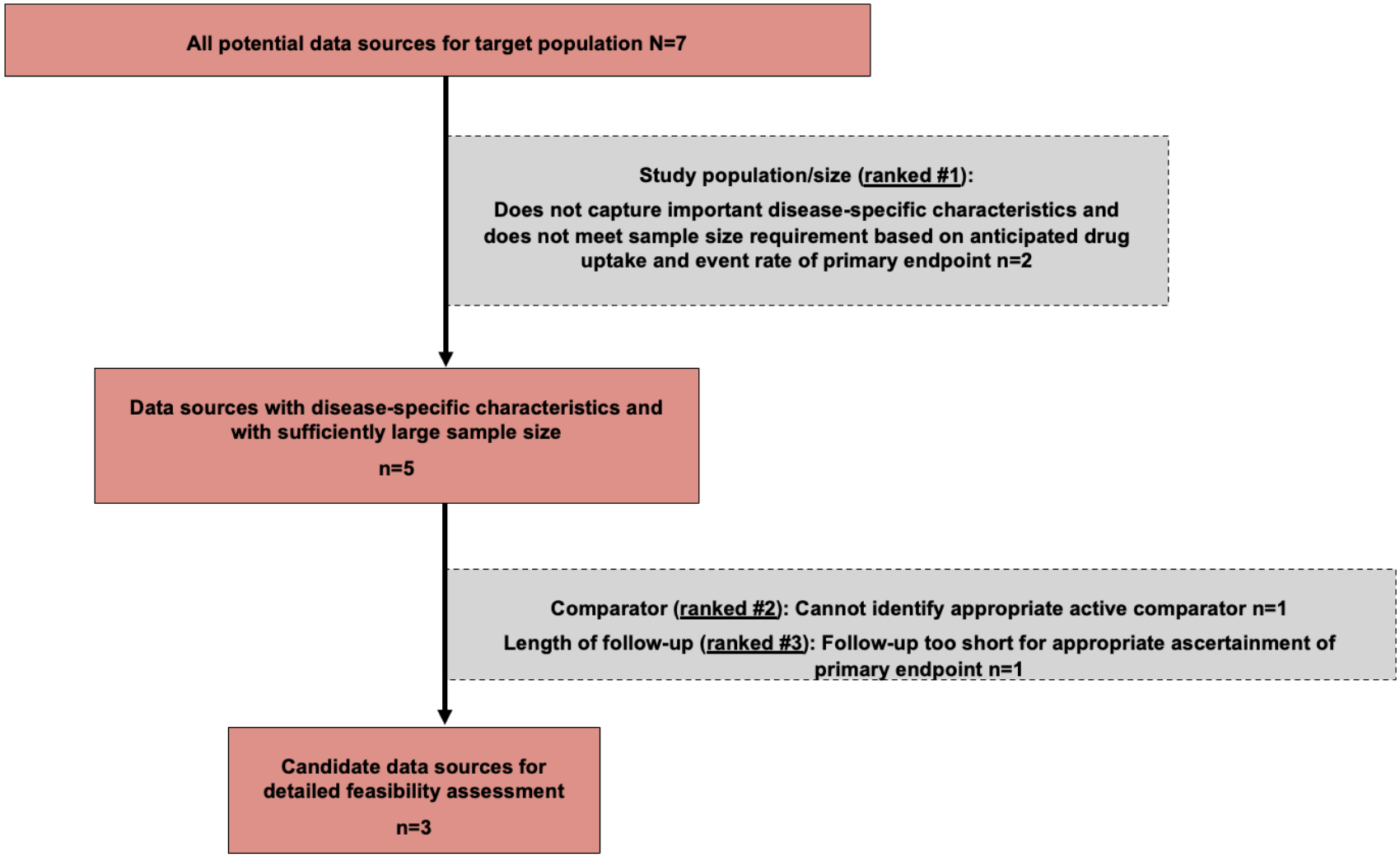
ICH M14 *Step 4*

Conceptual Framework for Generating Adequate Evidence using Real-World Data



Initial Feasibility Scan to Identify Fit-For-Purpose Data Sources (Steps 4-5)



Detailed Feasibility Assessment of Candidate Data Sources with Heatmap (Step 6)

	Data source 1	Data source 2	Data source 3
Study population - Ability to meet target sample size - Ability to capture important disease-specific characteristics	4	4	4
Identification of treatment group	5	5	5
Identification of active comparator group	5	3	3
Length and frequency of follow-up	4	3	3
Generalizability	5	2	2
Ascertainment of primary endpoint	4	3	3
Ascertainment of secondary endpoint	3	4	4
Historical use of data source for postmarketing commitments	4	4	4
Timelines - Time to fully executed contract, data access, and analysis	Fast	Slow	Slow
Final data source selection	SELECTED		

Legend: (5) Many or nearly all data requirements met (4) Several data requirements met (3) Likely that several data requirements met but requires further investigation (2) Some data requirements met or unable to assess at this time (1) Data requirements not met

Determine if Proposed Study, Including Selected Data Source(s), is Sufficient (Step 7a, 7b)

Data Source 1 selected. Further investigate availability of key elements of the secondary endpoint

Key elements of the secondary endpoint are available

Continue to Steps 8, 9, 10

If no existing data sources can be identified (e.g. rare disease), consider alternative approaches.

[See next slide]

Key elements of the secondary endpoint are missing

Evaluate alternative approaches

Can the missing data elements be collected by Data Source 1?

Is Data Source 1 still fit for use despite missing these key data elements?

Is linkage to another data source containing the missing data elements possible?

Add variables to existing registry

Consider *de novo* primary data collection

Return to Step 3

Iteration and Refinement

No data sources identified in feasibility assessment (Step 6)

Define specific data needs – specific measurement required to assess outcome: e.g. sexual maturity assessment using Tanner stage questionnaire

Choose alternative approaches: *De novo* primary data collection (e.g. registry) or hybrid approach (add questionnaire to existing data asset) (Step 7b)

Define study elements and evaluate the feasibility of each approach and choose approach (Steps 3-7a)

Develop protocol (Step 8)

Safety Reporting

Reporting of Adverse Events (AEs), Adverse Drug Reactions (ADRs) and product quality complaints

- **ICH E2D- Guidance for Market authorization holder (MAH) on reporting individual case safety reports (ICSRs)- "may require reporting to regulatory authority"**
- **Requirements can vary by:**
  - MAH, other sponsors, or applicant investigator.
  - Regions.
- **Refer to applicable laws and regulations (if ICH E2D not applicable).**

Study Reporting and Regulatory Submission

- **Consult guidance and engage early**
  - Refer to available guidance on document structure and content.
  - Initiate early discussions with regulatory agencies (agree on required documents and submission schedules).
- **Document variability (depending on local/regional requirements)**
  - Feasibility assessment
  - Protocol
  - SAP
  - Progress/interim and final reports
  - Reporting of AE / ADR / Product quality complaints
- **Leverage existing frameworks**
  - In the absence of specific regulatory guidance, use or adapt established frameworks from the scientific community.
    - For example: ISPE/ISPOR HARPER template

Dissemination and Communication

- **Public protocol availability**
  - Researchers are **encouraged** to make protocols publicly available in appropriate public registers of studies. This may be a regional requirement.
  - This should occur **after** protocol finalization.
- **Dissemination and communication of study results**
  - Registration of study reports may be required in accordance with local regulatory requirements.
  - Non-regulatory submission in scientific fora (e.g., conferences, workshops).
  - Peer-reviewed Scientific publications.
  - Communications tailored for patients and practitioners.
- **Leverage existing best practice recommendations for reporting studies in scientific literature**
  - **RECORD** (The Reporting of studies Conducted using Observational Routinely collected health Data).
  - **ENCePP** (The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance) - Guide on Methodological Standards in Pharmacoepidemiology.
  - **HMA-EMA** (Heads of Medicines Agencies – European Medicines Agency) - Catalogues of real-world data sources and studies.
  - **ICMJE** (International Committee of Medical Journal Editors) - Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.

Considerations for Guideline Implementation

- **Regional differences exist regarding:**
  - Patient privacy requirements;
  - Requirements for reporting adverse events;
  - Requirements for study reporting and record retention;
  - Data accessibility, readiness.
- **Other ICH guidelines to review in relation to ICH M14**
  - ICH E2D Post-Approval Safety Data Management
  - ICH E8 (R1) General Considerations for Clinical Studies
  - ICH E6(R3) Guideline for Good Clinical Practice
  - ICH E23 - Pursuing Opportunities for Harmonisation in Using Real-World Data to Generate Real World Evidence, with a focus on Effectiveness of Medicines (in development, reflection paper)

Additional Suggested Literature

- **It is beyond the scope of ICH M14 Guideline to provide detailed instruction for the design and execution of non-interventional safety studies.**
- **The Guideline provides references to literature providing additional detail on topics such as quantitative bias assessment and the design and conduct of studies on special populations.**

Conclusions

- **ICH M14 harmonises the general principles on planning, designing, analysing, and reporting of non-interventional studies.**
- **An iterative, data driven approach to identify fit-for-use data and to inform subsequent study design is provided.**
- **Goals include streamlining study design, facilitating submission of study protocols or reports across regulators, and supporting decision making.**

Contact

- **For any questions please contact the ICH Secretariat:**

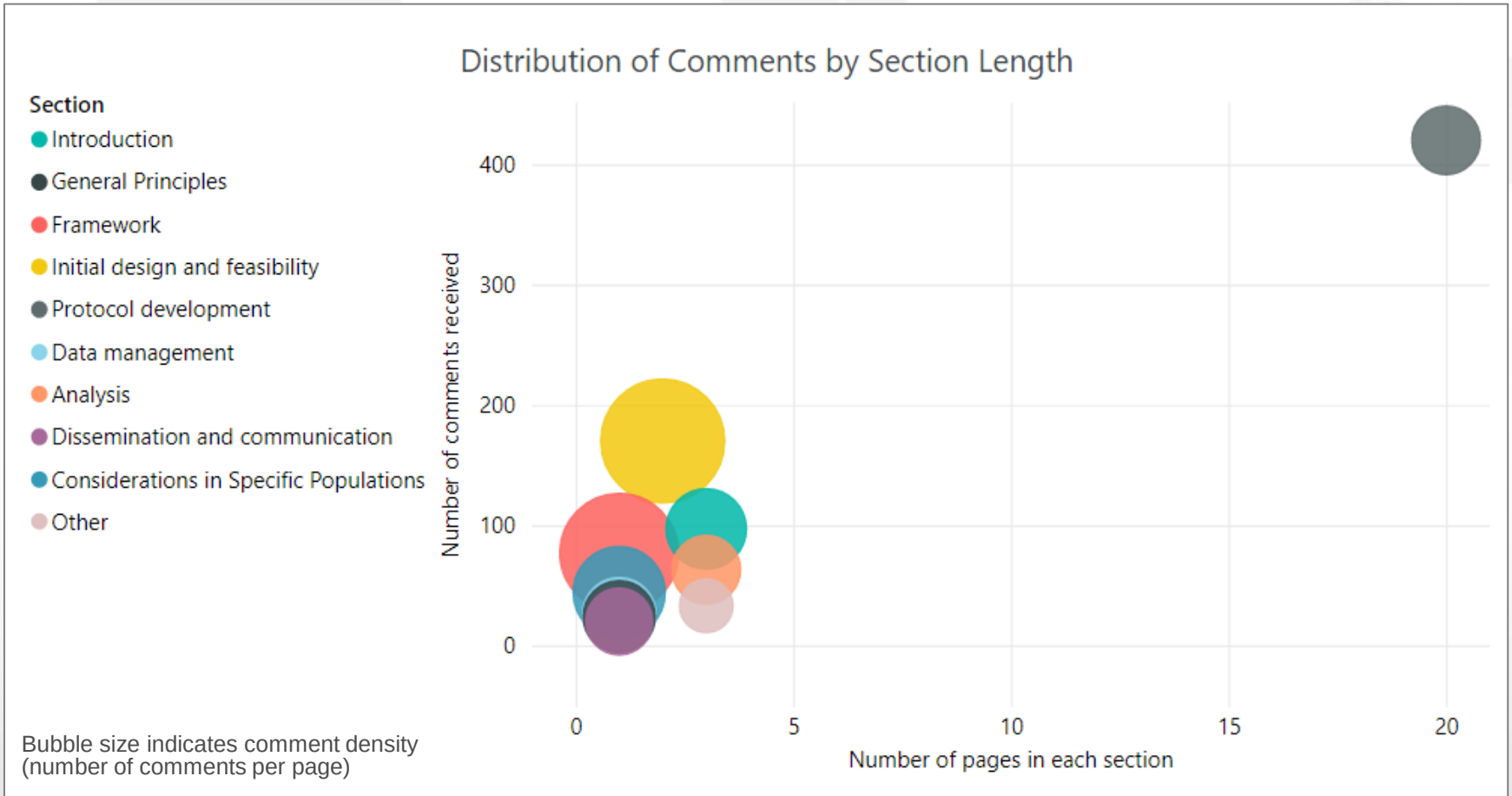
admin@ich.org

Appendix - Results of Public Consultation during Step 2b

Results of Public Consultation

- Strong interest from the community - approximately 1600 comments received
  - AI was used for the initial processing and deduplication (e.g., fuzzy matching and semantic clustering)

The figure below shows that, while “Protocol Development” section had the highest number of comments, it also had the highest number of pages. Sections “Initial Design and Feasibility” and “Framework” received a higher density of comments relative to their length.



Results of Public Consultation (cont.)

- Improvements to the guideline
  - Public comments resulted in changes to the guideline, incorporating more advanced methodological concepts and addressing a broader range of potential challenges in study design and execution.
  - Below is a visual summary of content areas where the guideline now provides additional detail or clarification.